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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/516,310	03/01/2000	Yao-Zhong Lin	22000.0021U2	3622

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EXAMINER	
SULLIVAN, DANIEL M	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 01/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	Application No. 09/516,310	Applicant(s) LIN ET AL.	
	Examiner Daniel M. Sullivan	Art Unit 1636	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 19 December 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *19 December 2005*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☒ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See Continuation Sheet*. (See 37 CFR 1.116 and 41.33(a)).
4. ☒ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *6 and 9-15*.
   Claim(s) withdrawn from consideration: *16-26 and 33*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☒ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☒ Other: Notice of non-compliant amendment.

DAVID GUZO
PRIMARY EXAMINER

Continuation of 3. NOTE: Newly added claim 39 is directed to the method of claim 6, wherein the signal peptide is selected from the SigPep database. As none of the previously examined claims recited this limitation, the claim raises new issues that would require further consideration to determine compliance under 35 USC §112, first paragraph..

Continuation of 11. does NOT place the application in condition for allowance because: First, Applicant is reminded that prosecution is closed in the instant application. Therefore, newly submitted evidence will not be considered without good and sufficient reason as to why it was not earlier presented.

With regard to the rejection under 35 USC §112, first paragraph, as lacking enablement, Applicant contends that the enabling disclosure need not teach the skilled artisan how to practice the claimed method such that a therapeutic outcome can be obtained because the claims do not recite that a therapeutic outcome is obtained. In sum, Applicant contends that the rejection is improper in focusing on results not recited in the claims and that all that is required to enable the claims is that the method provides the outcome of importation. In response, it is noted that the Examiner has not arbitrarily focused on therapeutic outcome. Rather, in seeking to determine whether the disclosure adequately teaches the skilled artisan how to make AND use what is claimed, the Examiner consulted the specification to determine how the inventor envisioned the practical application of the claimed method. As pointed out in previous Office Actions, the teachings of the specification with regard to using the claimed method are directed to therapeutic application and, for the reasons of record, it would require undue experimentation to further develop the method such that it could be used to provide a therapeutic outcome. If it is Applicant's position that the method is enabled in spite of the lack of enablement for therapeutic application because it can be used for practical applications other than therapy, Applicant should explicitly state what those applications are and where they are contemplated in the specification.

With regard to the Examiner's contention that the claims are not enabled for importation of any peptide, polypeptide or protein into any cell because the ability of an importation competent signal peptide to deliver any given peptide, polypeptide or protein into a cell would have to be determined on a case-by-case basis, Applicant contends that difficulties encountered in mobilizing proteins across the plasma membrane by mechanisms such as via pores, phagocytosis, endocytosis, invagination of the plasma membrane and cell surface-receptor mediated translocation are not relevant to the instant method because the mechanism by which the present method operates is different from these other mechanisms. Applicant's position is that any unpredictability evidenced by our understanding of these other processes is irrelevant to the operability of the claimed method because the mechanisms are different. This is a radical departure from the teachings of the specification, which bases the assertion that large proteins can be imported into cells by the claimed method on the export of large proteins from cells via the ER-golgi pathway.

Nevertheless, it is acknowledged that what is likely to be the mechanism of entry for importation competent signal peptides is distinct from the mechanisms that are understood in the art. However, what is clearly evidenced by the complexity of the known mechanisms of transporting polypeptides across membranes is that the plasma membrane is highly impermeable to proteins, and elaborate processes are typically required to move a protein across the plasma membrane. This is acknowledged in Applicant's specification in the paragraph bridging pages 1-2, which states, "Although the manufacture of known therapeutic peptides can be achieved by known methods, i.e., classic synthetic techniques or recombinant genetic engineering, DELIVERY OF THE PEPTIDES INTO A CELL HAS REMAINED PROBLEMATIC, SINCE THEY CANNOT READILY CROSS BIOLOGICAL MEMBRANES TO ENTER CELLS." Thus, it is well-established that the movement of any peptide, polypeptide or protein across a biological membrane is unpredictable. Therefore, the skilled artisan, based on the knowledge available in the art, would not expect that all peptides, polypeptides or proteins could be imported into a cell by the method claimed and would not know how to distinguish peptides, polypeptides or proteins that are operative in the method from peptides, polypeptides or proteins that are inoperative in the method.

Applicant cites a passage from Lindgren et al., which reads in full, "Peptide internalization often involves the formation of a channel, either in the plasma membrane or in the endosomes (following endocytosis and a pH shift from neutral to acidic). In the case of vector peptides, pore formation in the plasma membrane, as demonstrated for insect defensins [],is unlikely because it will provoke cell death. Internalization by endosome disruption or pore formation in the endosome, as shown for diphtheria toxin [], can be invoked for all peptides that bind a receptor and are not internalized at 4 C. However, the cell-penetrating peptides presented in this review are all internalized at 4 C, which excludes uptake by the classical endocytosis pathway (Box 1). In addition, their mechanism of cell entry appears to be protein independent." Applicant asserts that the teaching of protein independence provides evidence that essentially any peptide, protein or other molecule can be imported into cells using the claimed method. Applicant's position appears to be based on a misconception of the teaching. Lindgren teaches that "the mechanism of cell entry appears to be protein independent", which, viewed in context of the discussion of mechanisms of cell entry that require cellular proteins such as surface receptors or endocytotic proteins, is more likely a statement that the mechanism of entry does not involve cellular proteins rather than that a teaching that the properties of the cargo protein are irrelevant to transport across the plasma membrane.

Applicant also cites Veach et al. as teaching that chirally distinct forms of importation competent signal peptides are both equally capable of mediating importation of a peptide cargo and discusses possible mechanisms for transport that includes transport of charged cargo. Applicant urges that the teachings of Veach et al. actually support enablement for the claims because Veach et al. purports to have harnessed a signal-sequence derived hydrophobic region to deliver functional cargoes composed of peptides and proteins to probe and modulate intracellular signaling. However, the teaching that chirally distinct forms of importation competent signal peptides can import a single 10 amino acid peptide (see Figure 1A) and speculation as to a mechanism of entry does not obviate the fact that peptides, polypeptides and proteins have highly divergent chemical properties, and movement of any given peptide, polypeptide or protein across a biological membrane is unpredictable. The art of record does not provide a single substantiated example of a peptide, polypeptide or protein traversing a plasma membrane by the method claimed that is more complex than a 36 amino acid peptide. In view of the unpredictable and undeveloped state of the art as of the effective filing date of the instant claims, the limited teachings of Veach et al., published a decade later, do not suggest that the claims were enabled for the broad scope of a method of importing any peptide, polypeptide or protein into a cell in a subject at the time the application was filed.

With regard to the Examiner's contention that the disclosure is also not enabling for the method wherein the hydrophobic importation competent signal peptide is any importation competent signal peptide that meets the broad definition set forth in the specification, Applicant contends that the requirements of 35 USC §112, first paragraph, do not require that every peptide be named in the specification. Applicant asserts that a representative Group of signal peptides have been presented and the skilled artisan can choose from among them. Applicant is again reminded that the enabling specification must teach those skilled in the art to make and use the full scope of the claimed invention without undue experimentation. "Although not explicitly stated in section 112, to be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without "undue experimentation." Vaeck, 947 F.2d at 495, 20 USPQ2d at 1444; Wands, 858 F.2d at 736-37, 8 USPQ2d at 1404; In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (THE FIRST PARAGRAPH OF SECTION 112 REQUIRES THAT THE SCOPE OF PROTECTION SOUGHT IN A CLAIM BEAR A REASONABLE CORRELATION TO THE SCOPE OF ENABLEMENT PROVIDED BY THE SPECIFICATION)." In re Wright (CAFC) 27 USPQ2d 1510 at 1513. As discussed in previous Office Actions, the application seeks to claim a method of using any peptide comprising "a sequence of amino acids generally of a length of about 10 to 50 or more amino acid residues, many (typically about 55-60%) residues of which are hydrophobic such that they have a hydrophobic, lipid-soluble portion" (paragraph bridging pages 10-11 of the specification) and "'importation competent,' i.e., capable of penetrating through the cell membrane from outside the cell to the interior of the cell." However, in spite of the undeveloped and unpredictable state of the art at the time of filing, the application provides only a single working example of such a peptide and no specific guidance as to the structural characteristics that correlate with the function of importation competence. Applicant also asserts that the experimentation required to identify the operative embodiments of the importation competent signal peptides would be routine. However, as stated in the previous Office Action, given the tremendous scope of the claims and the absence of teachings that would enable the skilled artisan to identify those peptides having the function of an importation competent signal peptide, determining which embodiments that were conceived, but not yet made, would be inoperative or operative would clearly require expenditure of more effort than is normally required in the art.

With regard to the rejection of the claims under 35 USC §112, first paragraph, as lacking sufficient written description for the importation competent signal peptide of the claims, applicant asserts that the Examiner appears to be requiring the applicant to provide specific amino acid sequences of the signal sequences. However, no such assertion has been made. Applicant bases this interpretation on the Examiner's assertion that there is no clear nexus of structure and the function of importation competent signal peptides. Applicant seems to imply in the first paragraph on page 14 that the recitation "hydrophobic region" is the structural determinant that defines an importation competent signal peptide. However, if this were the case, any protein that comprises a hydrophobic peptide would be importation competent and would freely traverse biological membranes. As many proteins comprise hydrophobic regions yet few proteins are importation competent (Id.), the presence of a hydrophobic region does not correlate with importation competence.

Applicant further contends that the specification provides the example of the SN50 peptide and the SIGPEP database as species of the invention. In the paragraph bridging pages 14-15, Applicant states, "Applicants are contending that any of the signal peptides in the SIGPEP database could have been readily determined to be importation competent by one of skill in the art." However, Applicant is again reminded that the written description requirement of 35 USC §112 is severable from its enablement provision and a description of a method of identifying an importation competent signal peptide is not a description of the peptide itself (see, e.g., the first full paragraph on page 19 of the previous Office Action).

Finally, Applicant again asserts that the signal peptides of the instant claims are not new or unknown biological material that the skilled artisan would easily miscomprehend. Applicant contends that although the use of importation competent signal peptides was not known, the signal peptides themselves were known. However, the instant claims are directed to the use of "IMPORTATION COMPETENT SIGNAL PEPTIDES" not "signal peptides" in general, which is what Applicant asserts to be conventional in the art. As stated in Amgen Inc. v. Hoechst Marion Roussel Inc., 65 USPQ2d 1385, 1398 (CA FC 2003), "the [written description] requirement may be satisfied if in the knowledge of the art the DISCLOSED FUNCTION is sufficiently correlated to a particular, known structure. See Enzo Biochem, 296 F.3d at 1324, 63 USPQ2d at 1613" (emphasis added). For reasons set forth in previous Office Actions and herein, one of skill in the art would not have been able to correlate the function of an IMPORTATION COMPETENT signal peptide with a known structure at the time the application was filed.

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